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**Title:**

**2-[INDANYLAMINO]PYRIMIDONE AND  
2-[TETRAHYDRONAPHTHALENYLAMINO]PYRIMIDONE DERIVATIVES**

**Abstract:**

The invention relates to a pyrimidone derivative represented by formula (I) or a salt thereof: wherein R1 represents a hydrogen atom or a C1-6 alkyl group; R2 represents a hydrogen atom or 1 to 3 substituents selected from a C1-6 alkyl group, halogen atom, a C1-2 perhalogenated alkyl group, a C1-3 halogenated alkyl group, a hydroxyl group, a C1-6 alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C1-6 monoalkylamino group, C2-10 dialkylamino group; C0-6 alkylcarbonylamino group, C6,10 arylcarbonylamino group; R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C1-4 alkyl group, C1-4 alkoxy group or a halogen atom and n represents 0 or 1, when n represents 0 then m is 2 or 3, and when n represents 1 then m is 1 or 2. The invention relates also to a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3 beta such as Alzheimer's disease.

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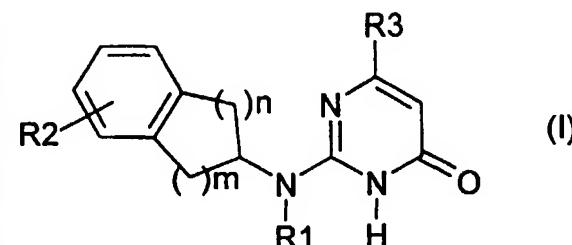
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(54) Title: 2-[INDANYLAMINO]PYRIMIDONE AND 2-[TETRAHYDRONAPHTHALENYLAMINO]PYRIMIDONE DERIVATIVES



(57) Abstract: The invention relates to a pyrimidone derivative represented by formula (I) or a salt thereof: wherein R1 represents a hydrogen atom or a C<sub>1-6</sub> alkyl group; R2 represents a hydrogen atom or 1 to 3 substituents selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, C<sub>2-10</sub> dialkylamino group; C<sub>6-10</sub> alkylcarbonylamino group, C<sub>6-10</sub> arylcarbonylamino group; R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom and n represents 0 or 1, when n represents 0 then m is 2 or 3, and when n represents 1 then m is 1 or 2. The invention relates also to a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3 $\beta$  such as Alzheimer's disease.

2-[INDANYLAMINO]PYRIMIDONE AND  
2-[TETRAHYDRONAPHTHALENYLAMINO]PYRIMIDONE DERIVATIVES

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Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of 10 neurodegenerative diseases caused by abnormal activity of GSK3 $\beta$ .

Background Art

GSK3 $\beta$  (glycogen synthase kinase 3 $\beta$ ) is a proline directed serine, 15 threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3 $\beta$  was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be 20 hyperphosphorylated in Alzheimer's disease and in several taupathies.

Interestingly, protein kinase B (AKT) phosphorylation of GSK3 $\beta$  results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3 $\beta$  of  $\beta$ -catenin, a protein involved in cell survival, results in its 25 degradation by an ubiquitination dependent proteasome pathway.

Thus, it appears that inhibition of GSK3 $\beta$  activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3 $\beta$ , enhances neuritogenesis in some models and also increases neuronal 30 survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that  $\beta$ -amyloid increases the GSK3 $\beta$  activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of  $\beta$ -amyloid are blocked by lithium chloride and by a 35 GSK3 $\beta$  antisense mRNA. These observations strongly suggest that GSK3 $\beta$  may be the link between the two major pathological processes in Alzheimer's disease : abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

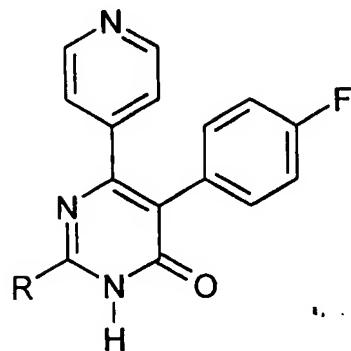
Although tau hyperphosphorylation results in a destabilization of the neuronal cytoskeleton, the pathological consequences of abnormal GSK3 $\beta$  activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect 5 survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that  $\beta$ -amyloid-induced increase in GSK3 $\beta$  activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

10 Altogether these experimental observations indicate that GSK3 $\beta$  may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a non- 15 limiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; 20 retinopathies and glaucoma.

In addition GSK3 $\beta$  may find application in the treatment of other diseases such as:

Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic 25 depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

PCT application WO 98/24782 discloses compounds represented by the following formula (A):



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wherein R represents a 2,6-dichlorobenzyl group, a 2-(2-chlorophenyl)ethylamino group, a 3-phenylpropylamino group, or a 1-methyl-3-phenylpropylamino group. The compounds represented by formula (A) are characterized by a 4-fluorophenyl group at the 5-position of the pyrimidine ring.

10 The main pharmacological activity disclosed for the compounds represented by formula (A) is an anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) herein below are useful as GSK3 $\beta$  inhibitors or as medicaments for the therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different.

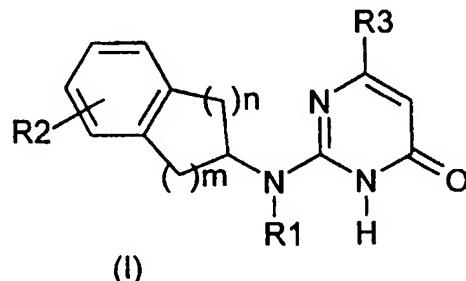
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#### Disclosure of the Invention

20 An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of the neurodegenerative diseases such as Alzheimer's disease.

25 Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3 $\beta$ . As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



wherein:

- 5 R1 represents a hydrogen atom or a C<sub>1-6</sub> alkyl group;
- R2 represents a hydrogen atom or 1 to 3 substituents selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, C<sub>2-12</sub> dialkylamino group,
- 10 C<sub>0-6</sub> alkylcarbonylamino group, C<sub>6,10</sub> arylcarbonylamino group;
- R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom; and
- n represents 0 or 1, when n represents 0 then m is 2 or 3, when n represents 1 then m is 1 or 2.

15 According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3 $\beta$  activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as:

- 20 25 Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.
- 30 As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease,

Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration);

5 brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

10 The present invention further provides an inhibitor of GSK3 $\beta$  activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

15 According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3 $\beta$  activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives 20 of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

25 As used herein, the C<sub>1-6</sub> alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-30 dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C<sub>1-6</sub> alkoxy group represents an alkyloxy group having from 1 to 6 carbon atoms, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-35 dimethylpropyloxy group;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C<sub>1-2</sub> perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogeno, for example a CF<sub>3</sub> or C<sub>2</sub>F<sub>5</sub>.

The C<sub>1-3</sub> halogenated alkyl group represents an alkyl group wherein at least one hydrogen has not been substituted by a halogeno,

The C<sub>1-6</sub> monoalkylamino group represents an amino group substituted by one C<sub>1-5</sub> alkyl group, for example, methylamino group, ethylamino group, 5 propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

The C<sub>2-12</sub> dialkylamino group represents an amino group substituted by two C<sub>1-5</sub> alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino 10 group;

The C<sub>0-6</sub> alkylcarbonylamino group represents an amino group substituted by a formyl group or a C<sub>1-6</sub> acyl group, for example, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group, hexanoyl group;

15 The C<sub>6-10</sub> arylcarbonylamino group represents an amino group substituted by a benzoyl group and a naphthylene carbonyl group.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals 20 and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as 25 lysine, δ-hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric 30 acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as 35 aspartic acid, and glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well known in the art which include, but are not limited

thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by 5 concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised 10 by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

15 In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, 20 and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

25 Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound may exist as tautomers. The existence of such tautomers is readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

30

Preferred compounds of the present invention represented by formula (I) include also:

35 (1) Compounds wherein R3 represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C<sub>1-2</sub> alkyl group, C<sub>1-2</sub> alkoxy group or a halogen atom.

More preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R3 represents a 4-pyridyl group which is not substituted;

5 (2) Compounds wherein n and m are 1.

(3) Compounds wherein R2 represents a hydrogen atom.

(4) Compounds wherein n, m and R2 are as defined under (2) and (3).

A particularly preferred compound is :

10 2-[(indanyl-2-yl)amino]-6-pyridyn-4-ylpyrimidin-4(1H)-one.

As a further object, the present invention concerns also methods for preparing the pyrimidone compounds represented by the aforementioned formula (I).

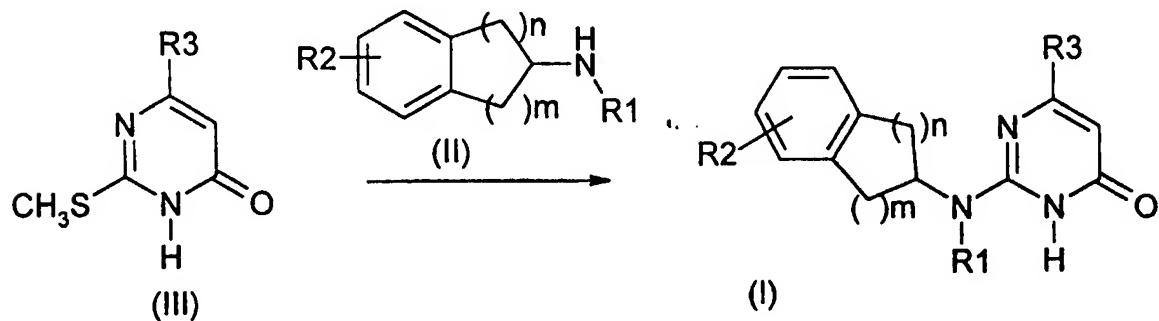
15 These compounds can be prepared, for example, according to methods explained below.

### Preparation method

Pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 1.

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Scheme 1



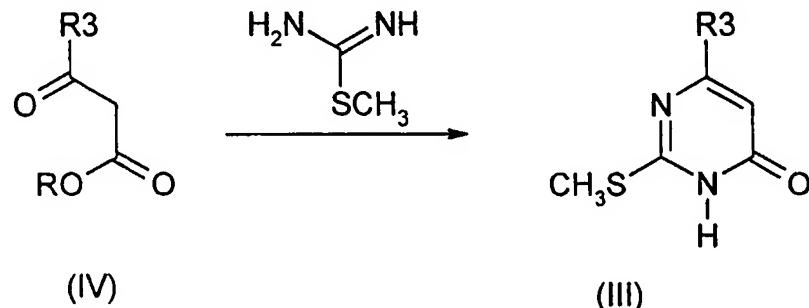
(In the above scheme the definition of R1, R2, R3, n and m are the 10 same as those already described above for compound of formula (I)).

The 2-methylthio derivative represented by the above formula (III) is allowed to react with an amine of formula (II) to obtain the compound of the aforementioned formula (I). The reaction may be carried out in a solvent such as, 15 for example, an alcoholic solvent such as n-pentanol or isoamyl alcohol at a suitable temperature ranging from 100 to 180 °C under ordinary air.

Compound of formula (III) may be prepared according to the method defined in scheme 2.

20

Scheme 2



(In the above scheme the definition of R3 is the same as already described for compound of formula (I) and R represents an alkyl.)

According to this method, the 3-ketoester of formula (IV) is allowed to react with a 2-methyl-2-thiopseudourea sulfate. The reaction may be carried out in solvent such as water or an alcohol, such as ethanol, propanol and butanol, at a suitable temperature ranging from 25-100°C under ordinary air.

5

Compounds of formula (II) and (IV) are commercially available or may be synthesized according to well-known methods of one skilled in the art.

For example compounds of formula (IV), wherein R3 represent a 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as a tetrahydrofuran at a temperature ranging from 20 to 70°C.

In addition when applicable, compound of formula (I) could be derivatised into other compound of formula (I), using well known methods in the art. This is the case, for example, when R1 or the substituent on the alkyl or alkoxy groups could be oxidized, hydrogenated, alkylated..., or be transformed using well known methods in the art to give another R1 or substituent within the scope of the present invention.

25

In the above reactions, protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group can be chosen depending on the type of a functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and deprotection methods are given for example in *Protective groups in Organic Synthesis* Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

35

The compounds of the present invention have inhibitory activity against GSK3β. Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases such as Parkinson's

disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration);

5 brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma; and other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

10

The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3 $\beta$  and of the aforementioned diseases which comprises administrating to a mammalian organism in need thereof an effective amount of a compound of the formula (I).

15

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The

20 substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the

25 aforementioned substances may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For

30 example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by

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dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

5        Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as  
10      pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

15      Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition  
20      may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for  
25      example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

30      Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations  
35      may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

## Chemical Examples

The present invention will be explained more specifically with reference to the following general examples, however, the scope of the present invention is 5 not limited thereby.

### Example 1 : Preparation of 2-[indanyl amino]pyrimidone and 2-[tetrahydronaphthalenyl amino]pyrimidone

#### 10 1.1. Preparation of Ethyl 3-(4-pyridyl)-3-oxopropionate

Isonicotinic acid (35.56 g, 289 mmol) was added to a solution of 1,1'-carbonylbis-1H-imidazole (46.98 g, 290 mmol) in tetrahydrofuran (700ml), and the resulting solution was stirred for 1.5 hr at 50°C. After cooling to room 15 temperature, malonic acid monoester potassium salt (51.7 g, 304 mmol) and magnesium chloride (34.33 g, 361 mmol) were added, and the mixture was refluxed for 1 hr and then heated at 50°C for 6 hr. The solvent was removed under reduced pressure and the residue was quenched by the addition of dilute acetic acid. The organic layer was extracted with ethyl acetate (3 times) and the 20 combined extracts were washed with dilute aqueous sodium bicarbonate and brine, and were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent ; hexane/ethyl acetate = 2/1 to 1/1) and recrystallization from hexane – ethyl acetate gave 41.52 g (74%) of the title compound.

25

#### 1.2 Preparation of 2-(Methylthio)-6-pyridinyl-4-ylpyrimidin-4(1H)-one

To a solution of 5.76 g (20.7 mmol) of 2-methyl-2-thiopseudouiurea sulfate in 48 ml of water was added 4.85 g (86.52 mmol) of potassium hydroxide. The mixture 30 was agitated and 8.0 g (41.4 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate was added and stirring was maintained for 48 hours.

The precipitate was recovered by filtration and was washed with water and then ether. The product was dried at 90°C in vacuo to give 6.26 g, 69% of white solid. Mp : 328-330°C.

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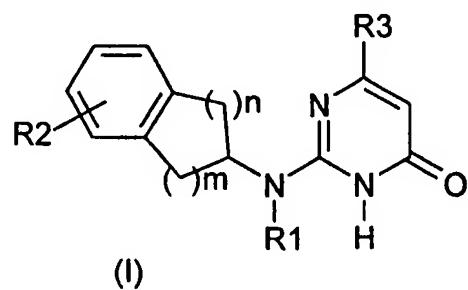
1.3 Preparation of 2-[indanyl amino]pyrimidone and  
2-[tetrahydronaphthalenyl amino]pyrimidone

A solution of 1 equivalent of 2-(methylthio)-6-pyridinyl-4-ylpyrimidin-4(1H)-one  
5 and 3 to 5 equivalents of 2-indanylamine or tetrahydronaphthalenylamine of  
formula (II) were suspended in amyl alcohol (0.1 - 0.2 M) and was heated at  
150°C during 72 hours. The cooled solution was concentrated and purified by  
chromatography on silica gel.

10 A chemical structure and physical data for a compound of the aforementioned  
formula (I) illustrating the present invention is given in table 1.

Table 1

15



20

N°	R1	R2	R3	n	m	m.p. °C	[M + H] <sup>+</sup>
1	H	H	4-pyridyl	1	1	223.1 – 223.2	305

**Test Example: Inhibitory activity of the medicament of the present invention against GSK3 $\beta$ :**

5 Two different protocols can be used.

In a first protocol : 7.5  $\mu$ M of prephosphorylated GS1 peptide and 10  $\mu$ M ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 10 7.5, 0.6 mM DTT, 6 mM MgCl<sub>2</sub>, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3 $\beta$ . (total reaction volume : 100 microliters).

In a second protocol : 4.1  $\mu$ M of prephosphorylated GS1 peptide and 42  $\mu$ M ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 15 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3 $\beta$ .

Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

20 The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P<sub>2</sub>O<sub>5</sub>), 126 ml 85% H<sub>3</sub>PO<sub>4</sub>, H<sub>2</sub>O to 500 ml and then diluted to 1 :100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution 25 described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.

The phosphorylated GS-1 peptide had the following sequence :  
NH<sub>2</sub>-YRRAAVPPSPSLSRHSSPHQS(P)EDEE-COOH.

30 The GSK3 $\beta$  inhibitory activity of the compounds of the present invention are expressed in IC<sub>50</sub>, and as an illustration, the IC<sub>50</sub> of the compound given in table 1 is of the order of 0.1 micromolar.

## Formulation Example

### (1) Tablets

5 The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
10 Lactose	200 mg
Magnesium stearate	4 mg

### (2) Soft capsules

15 The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

### 20 (1) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ampoule.

Compound of Example 1	3 mg
25 Sodium chloride	4 mg
Distilled water for injection	1 ml

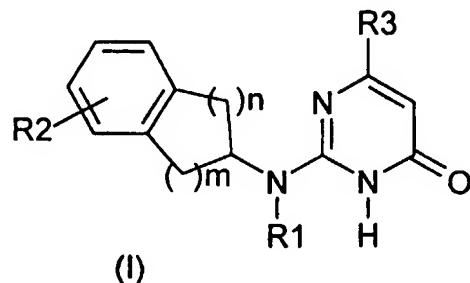
## Industrial Applicability

30 The compounds of the present invention have GSK3 $\beta$  inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3 $\beta$ .

What is claimed is:

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:

5



wherein:

R1 represents a hydrogen atom or a C<sub>1-6</sub> alkyl group;

10 R2 represents a hydrogen atom or 1 to 3 substituents selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, C<sub>2-12</sub> dialkylamino group ; C<sub>0-6</sub> alkylcarbonylamino group, C<sub>6,10</sub> arylcarbonylamino group;

15

R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom; and

n represents 0 or 1, when n represents 0 then m is 2 or 3, when n represents 1 then m is 1 or 2.

20

2. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1, wherein R3 represents an unsubstituted 4-pyridyl group.

25

3. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein n and m are 1 and R2 represents a hydrogen atom.

30

4. A pyrimidone derivative which is 2-[(indan-2-yl)amino]-6-pyridin-4-ylpyrimidin-4(1H)-one, or salts thereof, or a solvate thereof or a hydrate thereof.

5. A medicament comprising as an active ingredient a substance selected from a group consisting of a pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1.

5 6. A GSK3 $\beta$  inhibitor selected from the group of a pyrimidone derivative represented by formula (I) or salts thereof, or a solvate thereof or a hydrate thereof according to claim 1.

10 7. Use of a compound according to claim 1, 2, 3 or 4 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3 $\beta$  activity.

15 8. Use of a compound according to claim 1, 2, 3 or 4 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.

20 9. Use of a compound according to claim 8, wherein the disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies, vascular dementia; acute stroke, traumatic injuries; cerebrovascular accidents, brain cord trauma, spinal cord trauma; peripheral neuropathies; retinopathies or glaucoma.

25 10. Use of a compound according to claims 1 to 4 for the preparation of a medicament for preventive and/or therapeutic treatment of non-insulin dependent diabetes; obesity; manic depressive illness; schizophrenia; alopecia; or cancers.

30 11. Use according to claim 10 wherein cancer is breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia or virus-induced tumors.

## INTERNATIONAL SEARCH REPORT

Application No

PCT/EP 01/03636

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C07D401/04 A61K31/506 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application page 0; claims ---	1,2,5
A	CHEMICAL ABSTRACTS, vol. 83, no. 28, 1975 Columbus, Ohio, US; abstract no. 10127z, page 853; column 2; XP002145638 abstract & JP 07 435633 A (MORI, H.) 25 September 1974 (1974-09-25) ---	1,2,5
P,A	WO 00 18758 A (MITSUBISHI) 6 April 2000 (2000-04-06) claims; example 167; table 1 -----	1,2,5-11

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9824782	A 11-06-1998	AU 5525498	A	29-06-1998
		AU 733877	B	31-05-2001
		AU 6012098	A	29-06-1998
		BG 103512	A	31-07-2000
		BG 103521	A	31-07-2000
		BR 9713850	A	29-02-2000
		BR 9713863	A	14-03-2000
		CN 1246857	A	08-03-2000
		CN 1246858	A	08-03-2000
		CZ 9902015	A	17-11-1999
		CZ 9902016	A	17-11-1999
		EP 0948496	A	13-10-1999
		EP 0948497	A	13-10-1999
		HU 0001140	A	28-04-2001
		HU 0001698	A	28-04-2001
		WO 9824780	A	11-06-1998
		US 6096753	A	01-08-2000
JP 7435633	A	NONE		
WO 0018758	A 06-04-2000	AU 5759999	A	17-04-2000
		EP 1115721	A	18-07-2001